were discovering the ubiquity of cyclic organization of biochemical processes and the capacity of such cycles to provide auto-regulation of these processes. One of the first cycles proposed was by Otto Meyerhof, drawing upon the research of Archibald Hill on two periods of heat generation in muscle contraction, one accompanying formation of lactic acid during muscle contraction itself and the second accompanying the subsequent disappearance of lactic acid during a recovery phase (Hill, 1910; Hill, 1913). Meyerhof (1920; 1924) proposed a cycle, which he termed the *lactic acid cycle*, in which approximately three-quarters of the lactic acid formed during the anaerobic contraction phase was resynthesized to glycogen at the expense of the remaining molecules of lactic acid, which were further oxidized to carbon dioxide and water. As I will discuss in the next chapter, other proposals for cycles soon followed and as their ubiquity became clear, the question of why they occur so frequently arose. One reason is that they provide a means of regulation via such procedures as feedback control.[16] We saw an example of this in Figure 2.3. As another example, the cycle in which ATP is broken down to ADP and P_i in the course of muscle work and resynthesized during energy metabolism provides a means by which energy metabolism can be regulated to proceed only when ATP is needed for work.

Systems organized to regulate themselves are not unique to biology. Maintaining constant conditions is also important in many human artifacts and engineers have invented ways for doing so. Water clocks, for example, required that the water-supply tank be maintained at a constant level so that water ran out at a constant rate, and a feedback control system for such clocks was developed by Ktesibios in approximately 270 BCE. Windmills need to be pointed into the wind, and British blacksmith E. Lee developed the fantail as a feedback system to keep the windmill properly oriented. A temperature regulator for furnaces was developed by Cornelis Drebbel around 1624. Although each of these used a version of negative feedback, they were isolated developments limited to the machines in which they were utilized.[17] The governor developed by James Watt for his steam engine attracted much

[16] Mercer described the general consequence of such organization, which he attributed to James Danielli's "generalized cell theory": "The whole complex of enzymatically controlled reactions – in which the product of one reaction forms the substrate for the next, and often a final product is returned (or fed-back) to re-enter a cycle of reactions at another point – constitutes a system in dynamic equilibrium buffered against change, so long as material and energy is fed into it" (1962, p. 50).

[17] Harold Black's development in 1927 of negative feedback as a means of controlling feedback distortion in amplifiers such as those used in telephones – by feeding back the signal from the amplifier so as to compare it with the input signal – illustrates how the principle had to be rediscovered in each individual case.